

## **Research Protocol for Vanderbilt University Institutional Review Board Application for Human Research Health Sciences**

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Study Title: Nicotinic Treatment of Post-Chemotherapy Subjective Cognitive Impairment: A  
Pilot Study

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## I. Project Summary, Specific Aims, Background, & Significance

### a. Project Summary

This pilot study will obtain preliminary data regarding the use of transdermal nicotine treatment as a therapeutic strategy for persistent CRCI. This study will be a randomized, placebo-controlled pilot study to evaluate the effect of transdermal nicotine to 1) reduce subjective complaints and 2) enhance cognitive performance on laboratory measures of cognitive performance in breast cancer, colon cancer, lymphoma, or ovarian cancer patients with persistent CRCI. Participants will be randomized to either placebo or active compound (50/50) for the 6-week duration of the study. Participants will be assessed before, during, and at the end of treatment. At the end of the 8-week study, participants will have the option to take part in the open-label portion of the study for an additional 6 weeks.

### b. Specific Aims & Hypotheses

**Specific Aim 1: Assess if nicotine treatment will reduce subjective cognitive complaints in breast cancer, colon cancer, lymphoma, or ovarian cancer patients with persistent CRCI.**

Primary Hypothesis: Nicotine treatment will reduce subjective cognitive complaints in breast cancer, colon cancer, lymphoma, or ovarian cancer patients with persistent CRCI following 6 weeks of treatment.

**Specific Aim 2: Assess if nicotine treatment will enhance performance on laboratory measures of cognitive performance in breast cancer, colon cancer, lymphoma, or ovarian cancer patients with persistent CRCI.**

Secondary Hypothesis: Nicotine treatment will enhance cognitive performance on measures of attention and/or processing speed in breast cancer, colon cancer, lymphoma, or ovarian cancer patients with persistent CRCI following 6 weeks of treatment.

Exploratory Aims: As an exploratory analysis, a mixed-model ANOVA will be used to evaluate the effect of treatment group (nicotine, placebo) and *APOE* genotype (presence or absence of *APOE*ε4 allele) on change scores (Visit 2 to Visit 4) for the PCI FACT-Cog and each objective measure of cognitive performance. Differences for rates of adverse events or other safety abnormalities between groups will be assessed using chi-square analysis.

### c. Background:

Chemotherapy-related cognitive impairment (CRCI) is commonly reported following the administration of chemotherapy treatment in patients with cancer<sup>1</sup>. The American Cancer Society defines CRCI as: increased forgetfulness, trouble concentrating and remembering details, difficulty with multi-tasking word finding, and taking longer to finish tasks<sup>2</sup>. Although studies reporting cognitive impairments associated with chemotherapy have been reported since the 1980s<sup>3</sup>, the phenomenon commonly referred to as ‘chemo brain’ or ‘chemo fog’ is poorly understood<sup>4</sup>, and for some patients becomes the most distressful survivorship issue faced<sup>5</sup>. Advances in cancer treatment are producing a growing number of cancer survivors.

This is of particular importance for breast cancer survivors; the majority of women currently being diagnosed with breast cancer will be long-term survivors and will die of other, non-breast cancer related illness. The 5-year relative survival rate for women diagnosed with localized breast cancer is 98%, with 84% survival if the breast cancer involves regional lymph nodes<sup>6</sup>. Therefore, as the number of breast cancer survivors who have to cope with CRCI increases dramatically, it is crucial that we understand the cognitive impairments, the impact on survivors' functioning, and develop treatments for CRCI. While acute cognitive impairments *during* chemotherapy are fairly common<sup>7–9</sup>, studies have shown that these impairments persist for months or years in up to 35% of cancer survivors<sup>1,10–15</sup>. To date, most treatment studies have centered on treating side effects of chemotherapy such as fatigue<sup>16–19</sup> and anemia<sup>20,21</sup>, and have largely not focused on improving or treating cognitive symptoms associated with chemotherapy.

Investigators have proposed several models implicating that cancer treatment may modify the trajectory of normal cognitive aging<sup>4,22,23</sup> (Figure 1). The phase shift hypothesis postulates that cancer patients treated with chemotherapy will experience decline in cognitive function compared to non-cancer/chemotherapy treated persons, and that the trajectory of decline will parallel normal aging and will remain constant over time<sup>4</sup>. Alternatively, the accelerated aging hypothesis proposes that treatment with chemotherapy is accelerating the normal aging process<sup>23</sup>. This model predicts that the slope of cognitive decline will be steeper for cancer patients treated with chemotherapy compared to non-cancer/chemotherapy treated persons. Recent studies have suggested that older patients are more vulnerable to cognitive decline associated with chemotherapy<sup>24</sup> and tamoxifen<sup>25</sup>. Further, age appears to interact with predictors for future cognitive decline, such as cognitive reserve, to increase risk for cognitive decline following chemotherapy; older patients with low pretreatment cognitive reserve exposed to chemotherapy demonstrated reduced performance on measures of processing speed<sup>24</sup>. These models lead to the hypothesis that chemotherapy treatment should interact with factors that influence cognitive aging<sup>23</sup>.

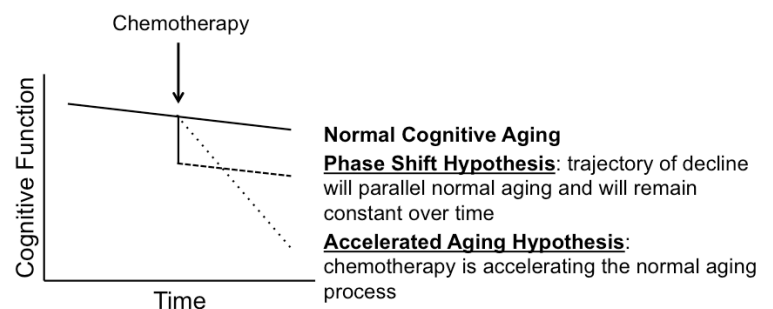


Figure 1. Possible interactions between chemotherapy and cognitive aging.

Although studies often find a lack of association between objective and subjective measures of cognitive function, there is increasing evidence that subjectively reported cognitive complaints, even with normal performance on cognitive tests, is associated with an increased risk for developing late-life cognitive decline and Alzheimer's disease (AD)<sup>26</sup>. Interestingly, there is a large amount of overlap between the types of objective impairments observed/subjective cognitive complaints commonly reported in patients with CRCI and cholinergically modulation cognitive functions (Table 1). Cognitive abilities such as attention, executive control, and memory rely heavily on the cholinergic neurotransmitter system<sup>27</sup>. Although changes across various domains have been reported for CRCI, effects have been reported most prominently in the domains of attention, working memory, executive function, and processing speed<sup>7,8,10–15,28–35</sup>. Recently, a study has shown that smoking history moderated the detrimental effect of the CRCI risk allele *APOEε4*<sup>36</sup> on cognitive performance

in breast cancer patients treated with chemotherapy, suggesting a link between nicotinic cholinergic system functioning and CRCI<sup>37</sup>. Given the potential link between the nicotinic cholinergic system and CRCI and the overlap between domains affected in CRCI and cholinergically modulated cognitive functions, the nicotinic cholinergic system represents a potential therapeutic target for improving cognitive functioning in breast cancer patients with CRCI.

The cholinergic system has been studied extensively in relation to cognitive aging and is the primary neurotransmitter system responsible for cognitive changes in both normal aging and dementia<sup>38</sup>. Given that cholinergic system integrity influences cognitive aging, it may interact with chemotherapy treatment. Cognitive abilities such as attention, executive control, and memory rely heavily on the cholinergic neurotransmitter system integrity, which modulates other neurotransmitter systems and overall cognition via nicotinic (and muscarinic) acetylcholinergic receptors<sup>27</sup>. The importance of the nicotinic cholinergic system was first understood using temporary blockade studies; antagonist drugs such as mecamylamine result in performance deficits across several cognitive domains, such as learning, memory, psychomotor speed, and attention<sup>39,40</sup>. Drugs that stimulate the nicotinic cholinergic system have the opposite effect, acting as cognitive enhancers<sup>41</sup>. A recent meta-analysis of over 41 double-blind placebo-controlled laboratory studies by Heishman and colleagues concluded that there are significant positive effects of nicotinic stimulation with nicotine on motor abilities, attention, and memory<sup>41</sup>.

Nicotinic agonists have been shown to improve cognitive performance in several clinical populations with cognitive impairment, including AD<sup>42–46</sup>, mild cognitive impairment (MCI)<sup>47</sup>, and attention deficit hyperactivity disorder (ADHD)<sup>48</sup>. However, nicotine has not been explored as a potential treatment for CRCI in the breast cancer population. Studies have shown that nicotinic agonists may exert differential effects on domains of cognition; certain cognitive domains tend to see more benefit than others<sup>48,49</sup>. The pattern of response to nicotine may follow an inverted 'U' shape model<sup>50</sup>, where nicotinic treatment tends to improve performance only in those with some level of baseline impairment, and can actually decrease performance in otherwise healthy individuals. Therefore, breast cancer patients with *persistent* CRCI (continued impairment 1-5 years post chemotherapy) may derive therapeutic benefit from nicotine treatment compared to those without cognitive impairment.

#### **d. Significance:**

This proposed study has broad clinical and scientific significance. If the hypotheses were validated, these findings would support a novel, broadly available, and inexpensive intervention for persistent CRCI and would encourage early treatment intervention to improve subjective cognitive complaints and/or cognitive performance and could have significant benefits for large numbers of cancer survivors. This would be the first trial of nicotine or nicotinic agonists to date in CRCI.

## **II. Inclusion/Exclusion Criteria**

**a. Sample Size**

We used average pre-chemotherapy and post-chemotherapy FACT-Cog scores (provided by Dr. Lynne Wagner) to estimate an expected effect size (Pre-chemotherapy mean= 64.57, SD=12.16; Post-chemotherapy mean= 58.51, SD=14.55; Effect size  $d=0.44$  or  $f=0.23$ ). Based on the data provided, we would need 32 participants to see and effect size of  $f=0.23$ . Based on previous nicotine treatment studies conducted by the lab we anticipate a dropout rate of 10-20%<sup>47</sup>; therefore we will target recruitment at 40 participants.

**b. Inclusion Criteria:**

All participants will:

1. Be between 35 and 80 years of age,
2. Have been diagnosed with noninvasive or invasive (Stage 1, 2, or 3A) breast cancer, colon cancer, lymphoma, or ovarian cancer
3. Have undergone treatment with systemic chemotherapy within the last 1-5 years,
4. Endorse persistent CRCI subjective complaints (as defined below),
5. Be non-smokers (no nicotine use within the last 5 years),
6. Have no active cardiac, neurologic, or psychiatric illness, and
7. Fluent in and able to read English.

**c. Exclusion Criteria:**

Participants will be excluded for:

1. Any active neurologic psychiatric disease, clinically significant cognitive impairment or dementia, history of significant head trauma followed by persistent neurologic deficits, or known structural brain abnormalities,
2. Current major depression or another major psychiatric disorder as described in DSM-5 (use of CNS active medications (e.g. antidepressants) will be permitted, provided dosing has been stable for at least 3 months),
3. Any history of alcohol or substance abuse or dependence within the past 2 years (DSM-5 criteria),
4. Any significant systemic illness or unstable medical condition which could lead to difficulty complying with the protocol including:
  - 4a. History of myocardial infarction in the past year or unstable, severe cardiovascular disease including angina or CHF with symptoms at rest, or clinically significant abnormalities on the ECG
  - 4b. Active vascular disease or medical conditions that per Investigator opinion can interfere with participant's safety and treatment
  - 4c. Clinically significant and/or unstable pulmonary, gastrointestinal, hepatic, or renal disease
  - 4d. Insulin-requiring diabetes or uncontrolled diabetes mellitus,
  - 4e. Uncontrolled hypertension (systolic BP > 170 or diastolic BP > 100),
5. Use of any investigational drugs within 30 days or 5 half-lives, whichever is longer, prior to screening, and
6. Use of any drugs with pro-cholinergic properties (e.g. donepezil). Use of anticholinergic agents will be discouraged, but will be reviewed on a case-by-case basis by the PI.

## 7. Females who are pregnant or nursing

### III. Study Design

This study will be a randomized, placebo-controlled pilot study to evaluate the effect of transdermal nicotine to 1) produce positive effects on subjective complaints and 2) enhance cognitive performance on laboratory measures of cognitive performance in breast cancer, colon cancer, lymphoma, or ovarian cancer patients with persistent CRCI. Participants will be randomized to either placebo or active compound (50/50) for 6-weeks, followed by 2 weeks of treatment withdrawal (for a total of 8 weeks). Participants will be assessed both pre-, during, and post- treatment. At the end of the 8-week study, participants will have the option to take part in the open-label portion of the study for an additional 6 weeks (explained below).

**Table 2. Summary of Study Visits**

Visit 1	Visit 2	Randomization (nicotine/placebo)	3 Weeks of Treatment	Visit 3	3 Weeks of Treatment	Visit 4	2 Weeks NO Treatment	Visit 5
Screening	Baseline Assessment			Repeat Assessment		Repeat Assessment		Repeat Assessment

#### Pre-Screening

Prior to consent, participants will be pre-screened to determine the participant's preliminary eligibility for the study. Participants will be emailed a link to a RedCap form that asks the participant to provide the following information: demographics, contact information, SSN (SSN is required if the participant has not been previously seen at Vanderbilt University to create a medical record in Star Panel so Visit 1 can be scheduled at the Clinical Research Center), social and medical history, cancer history, concurrent medication, use of tobacco, alcohol, drug, head trauma, and behavioral concerns. Once the pre-screening form is filled out, it will be reviewed by Jennifer Vega, Study Coordinator and Paul Newhouse, MD to determine preliminary eligibility for the study.

### IV. Double-Blind Study Visits

#### 1. Screening (Visit 1)

**Participant Screening:** Initial screening of recruited participants will be performed by the study coordinator (JNV). Following initial screening, a review of medical records will be conducted to ensure good general health. Review of cancer medical records will be done to confirm that the participant meets the criteria for breast, colon cancer, lymphoma, or ovarian cancer and systemic chemotherapy. Information on allergies, all current medications, and present and past use of tobacco, alcohol, and illicit drugs will be collected. Participants will be cognitively and behaviorally screened to rule out dementia. Electrocardiogram (ECG) and blood draw for laboratory tests (FSH and DNA) screening will take place at the Vanderbilt Clinical Research Center (CRC) or the Center for Cognitive Medicine (CCM). The screening packet including medical history, cancer medical records, ECG, cognitive testing, behavioral screening, and consent form will be reviewed by the study physician for approval prior to study entry.

**Cognitive Screening Measures:** All participants will be screened to exclude individuals with evidence of clinically significant cognitive impairment or dementia. Participants will be evaluated using the Wechsler Abbreviated Scale of Intelligence (WASI), Mini Mental State Exam (MMSE; score  $\geq 26$ ), Brief Cognitive Rating Scale (score  $\leq 2$ ) and the Mattis Dementia Rating Scale (minimum score 125) to establish a Global Deterioration Scale score (GDS; score  $\leq 1$ ) which rates the degree of cognitive impairment. To rule out the presence of current mood disorders, all participants will be psychiatrically assessed using a portion of the Structured Clinical Interview (SCID) for DSM disorders, the Beck Depression Rating Scale (BDI), and the Beck Anxiety Inventory (BAI). Information obtained from the BDI and/or BAI may be used as potential covariates in data analysis. The Short Form-36 Health Survey (SF-36)<sup>51</sup> will be used to evaluate health and somatic complaints. The Adult Self-Report (ASR; for participants  $\leq 59$  years of age) or the Older Adult Self-Report (OSAR; for participants  $\geq 60$  years of age)<sup>52</sup> will be used to rule out presence of other psychopathology and to assess difficulty or impairment in instrumental, occupational, or social functioning. Participants will also fill out a Menopause Symptom Checklist to assess menopausal status. REDCap will be used to collect the SF-36, Menopause Symptom Checklist, BDI and BAI.

**Defining persistent CRCI:** We recognize that the definition for CRCI is evolving, but for the purposes of the current study we will define persistent CRCI as follows: 1) endorsed change in cognitive functioning (self-report) the participant directly links to chemotherapy treatment received in the last 1-5 years, 2) evidence of subjective impairment on the Cognitive Complaint Index (see below), and 3) subjective complaints not better accounted for by presence of depression and/or another psychiatric or neurologic condition.

The Cognitive Complaint Index (CCI; Visit 1)<sup>26</sup> will be used to operationalize breast, colon cancer, lymphoma, or ovarian cancer patients as having subjective complaints as follows: All participants will complete the multiple inventories that comprise the CCI on REDCap, including the Memory Functioning Questionnaire<sup>54</sup>, Memory Self-Rating Questionnaire<sup>55</sup>, the Neurobehavioral Function and Activities of Daily Living Rating Scale (ADL-self)<sup>56</sup>, the Informant Questionnaire on Cognitive Decline in the Elderly (IQCDE)<sup>57</sup>, the 30 items from the Geriatric Depression Scale (GDS)<sup>58</sup>, 12 items from a telephone-based screening for mild cognitive impairment (MCI), and 20 items from the Memory Assessment Questionnaire adapted in part from the Functional Activities Questionnaire<sup>59</sup>. A CCI score will be calculated as the percentage of all items endorsed. Participants must show a CCI that includes endorsement of at least 20% of all items to be considered as having chemotherapy-related subjective complaints.<sup>26</sup>

**DNA Sample Collection for APOE Genotyping:** From each participant, a nurse at the CRC or CCM will perform a blood draw and will obtain a whole blood sample of 7mL total volume from a trained phlebotomist using one 7mL Vacutainer tubes with K<sub>3</sub>EDTA. This purple-top tube will be sent to the Vanderbilt DNA Resources Core and will be processed for DNA extraction, quantification, and banking. DNA extractions will be performed on one of the Gentra Systems AutoPure automated DNA extraction system in the Vanderbilt DNA Resources Core. The genetics core will request a re-sampling if the sample condition is compromised or if there is poor sample yield.



Once approved for the study, participants will be asked to come in for 4 additional study visits, which will each last 2-3 hours each. Participants will also be randomized to receive either nicotine or placebo patch after, which they will begin after completing their baseline assessment.

## 2. Baseline Assessment (Visit 2)

- a. **Subjective Measure:** The Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog)<sup>59</sup> (either the written form or the REDCap version) scale will be used to monitor change in CRCI subjective complaints. This instrument has been used to monitor change in CRCI subjective complaints in previous studies and demonstrates good internal consistency, test-retest reliability, and discriminant and convergent validity<sup>60–62</sup>. This 37-item questionnaire is a self-report measure of cognitive function that aims to evaluate the “real world” impact of CRCI. It consists of four subscales (PCI: Perceived Cognitive Impairments, PCA: Perceived Cognitive Abilities, QOL: Impact on quality of life, and Oth: Comments from Others) and evaluates memory, concentration, mental acuity, verbal fluency, functional interference, and multitasking ability. Higher scores indicate better cognitive functioning.
- b. **Objective Performance Measures:** To characterize the effects of nicotine on cognitive functioning in breast cancer, colon cancer, lymphoma, or ovarian cancer patients with persistent CRCI, we will utilize measures that meet one or more of the following criteria: 1) target domains most likely to be endorsed by patients with persistent CRCI (i.e. attention, working memory, executive function, and processing speed) and/or 2) prior demonstration of response to nicotinic stimulation or blockade in nicotine studies. Our cognitive performance battery (Table 3) will consist of subtests from the CogState battery and other computerized and verbal tests. The CogState battery (CogState Ltd., Melbourne, Australia) is comprised of a subset of tasks that includes measures of various cognitive domains<sup>63</sup> (see Table 3). The tasks in the CogState battery have been specifically designed to assist with decisions about the presence or absence of cognitive change. The tests chosen in this battery were selected to specifically target the domains most likely to be endorsed by breast cancer patients with persistent CRCI and because they are brief and can be given repeatedly without eliciting practice effects over time<sup>64,65</sup>. Other computerized tasks such as the Critical Flicker Fusion (CFF) task,<sup>66</sup> the Choice Reaction Time (CRT) task<sup>67</sup>, and the Conners Continuous Performance Test (CPT) will also be given.<sup>68,69</sup> We have previously found the CPT to be sensitive to nicotine-induced attentional improvements in people with ADHD, AD<sup>70</sup>, healthy young adults<sup>71</sup>, and in nicotine-treated MCI patients<sup>47</sup>; improvements in performance on this task have been shown to correlate with clinical improvement. The Buschke Selective Reminding Task (SRT) will be used to assess immediate and delayed memory recall. The battery is expected to take 2-3 hours.

**Table 3. Summary of Subjective and Objective Cognitive Performance Measures**

Subjective Measure	Administration	
Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog)	Self-Report	Consists of four subscales (PCI: Perceived Cognitive Impairments, PCA: Perceived Cognitive Abilities, QOL: Impact on quality of life, and Oth: Comments from Others)
Objective Measures	Administration	Cognitive Domain/Function
Groton Maze Learning Test	CogState Battery (Computerized)	Executive Function/ Spatial Problem Solving
Set-Shifting Task		Executive Function
Detection Task		Psychomotor Function/ Speed of Processing
Identification Task		Visual Attention/Vigilance
One Back Task		Attention/Working Memory
Two Back Task		Attention/Working Memory
CPT	Computerized	Sustained Attention/Vigilance
CRT		Attention /Psychomotor Speed
CFF		Attention/Vigilance
Buschke SRT	Verbal	Immediate/Delayed Memory Recall

If a participant is pre-menopausal and of childbearing age, they will be required to take a urine pregnancy test prior to randomization (Visit 2) and at each subsequent visit throughout the study (Visits 3, 4, 5, 6, 7). Post-menopausal participants are not required to take a pregnancy test. If at any point the participant believes they may be pregnant, they will be advised to discontinue use of the study medication and inform the study coordinator immediately.

### 3. 6-Week Treatment Period

Nicotine will be delivered by a transdermal patch delivery system for topical application, available in sizes of 10, 20cm<sup>2</sup>. Each patch will contain approximately 1.75mg nicotine/cm<sup>2</sup>, and releases 7, and 14mg of nicotine, respectively, over 24 hours. Participants will be randomized (50/50) to receive either blinded nicotine or placebo skin patches. A random number generator will be used to assign participants to either the treatment or placebo group. The titration administration pattern will be as indicated in Table 4 to help to avoid initial side effects.

**Table 4. Drug Titration Schedule**

Week(s)	Dose
Week 1	½ 7 mg patch per day (for 16 hours per day)
Week 2	7 mg patch per day (for 16 hours per day)
Weeks 3-4	¾ 14 mg patch per day (for 16 hours)
Weeks 5-6	14 mg per day (for 16 hours)
Weeks 7-8	Treatment withdrawal

Patches will be applied for 16 hours per day. Participants will be contacted by phone weekly to assess tolerability and answer questions. If a participant appears to be suffering persistent side effects at any dose, they will not be titrated to the next highest dose until they are free of side effects. Participants will be followed-up with 2-weeks after withdrawal of treatment at the end of the study to evaluate any residual effects of the nicotine or nicotine withdrawal symptoms. At the end of the study, if a participant would like to continue utilizing transdermal nicotine because of perceived cognitive benefits, the participant will be referred to their primary physician or another appropriate physician for management.

#### **4. Visits During Treatment (Visits 3 and 4)**

Visits 3 will take place after 3 weeks of treatment and Visit 4 will take place after 6 weeks of treatment. The battery in Table 3 will be repeated for Visits 3 and 4. After Visit 4 will be asked to stop using the nicotine or placebo patches for 2 weeks.

#### **5. Visit after 2 weeks of treatment withdrawal (Visit 5)**

Visit 5 will take place after 2 weeks of treatment withdrawal and will involve a repeat of the battery in Table 3 completed during previous visits.

### **V. Open-Label Extension**

At the end of the double blind, placebo controlled 8-week study participants will have the option to take part in the open-label portion of the study for an additional 6 weeks. Since we will not know which condition (nicotine or placebo) the participant was randomized to during the blinded portion of the study, all participants will be treated as though they received placebo and will follow the titration administration pattern will be as indicated in Table 4 to help to avoid initial side effects. Patches will be applied for 16 hours per day. Participants will be contacted by phone weekly to assess tolerability and answer questions. If a participant appears to be suffering persistent side effects at any dose, they will not be titrated to the next highest dose until they are free of side effects. During this time, participants will come in for 2 additional study visits, during which we will collect safety data (heart rate, respiration, blood pressure, and temperature) and FACT-Cog scores (see figure below). Each visit will take approximately 30 minutes. At the end of the open label portion of the study, if a participant would like to continue utilizing transdermal nicotine because of perceived cognitive benefits, the participant will be referred to their primary physician or another appropriate physician for management. Participants that are pre-menopausal and of childbearing age will be required to take a urine pregnancy test prior to beginning the Open-Label portion of the study (Visit 5) and throughout the duration of the Open-Label portion of the study (Visits 6 and 7). If you are post-menopausal, a pregnancy test will not be required. If at any point you believe that you are pregnant, you should discontinue use of the study medication and inform us immediately.

Table 5. Summary of Open-Label Extension Visits

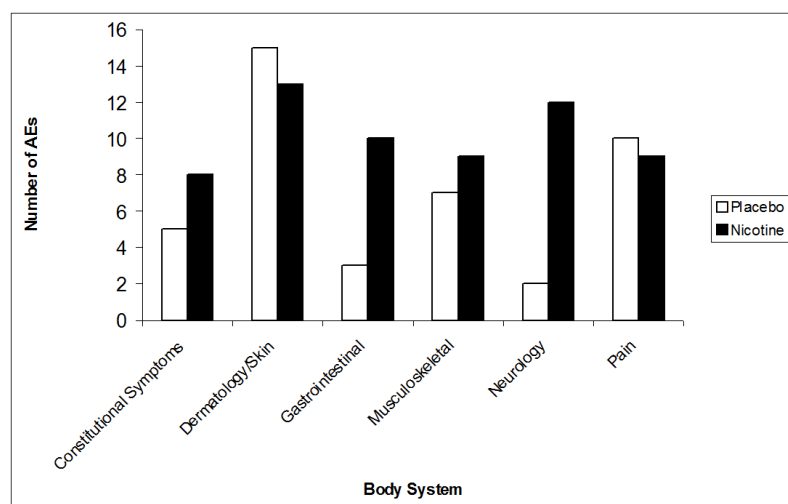
3 Weeks of Treatment	Visit 6	3 Weeks of Treatment	Visit 7
	Safety Data & FACT-Cog		Safety Data & FACT-Cog

## VI. Potential Risks/Drug Safety: Nicotine Transdermal Patch

**Side Effects of Nicotine:** At the nicotine doses proposed in this study, the major peripheral action of nicotine is facilitation of impulses through all autonomic ganglia, stimulation of the adrenal medulla and stimulation of sensory receptors including chemoreceptors in the carotid body. Ganglionic depression occurs at higher nicotine levels. In cardiovascular systems, mild increases in heart rate and blood pressure from sympathetic ganglion stimulation, catecholamine release from adrenal medulla, and aortic and carotid body chemoreceptor stimulation may occur. A mild parasympathetic response may be seen in the gastrointestinal tract and bladder (increased tone and motor activity), with increased secretion of exocrine glands. Nausea and vomiting can occur from peripheral (bowel activity and vagal efferent nerve stimulation) and central (medullary emetic chemoreceptor trigger zone stimulation) causes. Low dose stimulation of the CNS could in theory produce tremors and respiratory stimulation, although this is rarely seen except in patients with tremor disorders. Toxic nicotinic doses result in CNS depression. With use, tolerance develops to virtually all acute adverse effects.

**General Safety Experience with the Nicotine Transdermal Patch:** A large meta-analysis was conducted examining data from 35 clinical trials utilizing the transdermal nicotine patch in over 5500 individuals<sup>72</sup>. Few adverse cardiovascular outcomes were reported and no excess of these outcomes was detected among patients assigned to nicotine patch use compared to placebo patch users. Minor adverse effects such as sleep disturbances, nausea, localized skin irritation, and respiratory symptoms were elevated in patch users compared to placebo users.

*Adverse events from our recently published MCI trial (**conducted in non-smoking individuals**) are presented in Figure 2. Total adverse events (AEs) for the double-blind treatment period were 82 for nicotine versus 52 for placebo ( $p < 0.05$ ). **However, the majority of AEs were mild (nicotine 57.3 %; placebo 54.9%) and there was no statistically significant difference in the proportion of adverse events within the different severity classifications between treatments (Mann-Whitney test  $p = 0.97$ ). No severe AEs were classified as related to drug treatment in either treatment group. Adverse event rates by body systems reported in more than 10% of subjects were***



**Figure 2. Adverse event numbers from MCI pilot trial. Vertical axis is total AE reports for each system/category**

comparable with the exception of “gastrointestinal” (virtually all mild nausea within the first week) and neurological (virtually all mild headache or dizziness in the first 2 weeks) for which there were more AEs reported in the nicotine-treated group. **Approximately 75% of AEs in both placebo and nicotine groups were judged not related or doubtfully related to treatment.** Four nicotine-treated subjects discontinued treatment for adverse events vs 0 placebo-treated subjects ( $p=0.05$ ). No withdrawal symptoms were reported by subjects or informants nor were any subjects reported to be continuing to use nicotine after the study was completed.

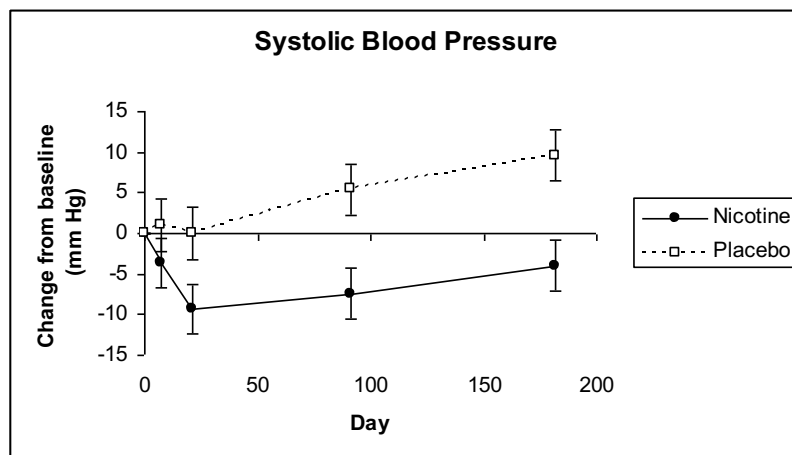
**Dermatologic Safety:** The most common adverse side effect of the nicotine transdermal patch is skin irritation and accounted for approximately 25 percent of adverse event reports regarding the nicotine transdermal patch to the FDA<sup>73</sup>. These effects consist of erythema, pruritus, edema, and rash. Mild skin irritation is common and generally occurs after three weeks of continuous use. Mild to moderate reddening of the skin is seen in 25% of subjects and transient itching in 29%. More severe reactions requiring modification of treatment have been reported in up to 12% of users (DrugDex Drug Evaluation Monograph). Management of the symptoms is usually straightforward and is accomplished by patch rotation, local treatments, and instructing the patient to remove the patch prior to going to bed.

**Cardiovascular Safety:** There are a number of mechanisms whereby nicotine could potentially cause or aggravate cardiovascular disease<sup>73</sup>. Nicotine stimulates CNS sympathetic systems and increases release of catecholamines from both the adrenal and vascular nerve endings. While tolerance appears to develop to these cardiac stimulatory effects, the tolerance developed is only partial<sup>73</sup>. While there may be a small chronic cardio-stimulatory effect (approximately seven beats per minute), the dose response curve appears to be flat<sup>73</sup>.

However, studies have not demonstrated that nicotine replacement therapies are associated with increased cardiovascular risk or increased incidence of cardiovascular adverse events (DrugDex Drug Evaluation Monograph). The largest and longest such study was the Lung Health Study that enrolled almost 6000 individuals in a study over 5 years involving nicotine replacement therapies for smoking cessation. In this group with chronic lung disease, nicotine use was found to be marginally protective of cardiovascular health compared to non-use of nicotine<sup>73</sup>. This protective effect persisted even when adjusted for smoking status. Even within the ex-smoking sub-group in the same study, nicotine users had substantially lower rates of hospitalization than non-users. Nicotine also showed a marginally protective

effect against peptic ulcer disease in the same subjects. In a long-term maintenance study of non-smoking patients with ulcerative colitis, there were no increased cardiovascular events and markers of cardiovascular risk either did not change or actually decreased (e.g. fibrinogen)<sup>73</sup>. A recent investigation of the effects of 26 weeks of chronic oral nicotine showed improved cardiovascular risk parameters (e.g. capillary flow, fibrinogen) after smoking cessation with no negative effects of nicotine<sup>74</sup>. Nicotine does not appear to promote thrombosis or platelet aggregation nor does nicotine replacement therapy increase the risk of acute myocardial infarction (DrugDex Drug Evaluation Monograph).

Studies of patients with known cardiovascular disease have similarly not shown an increase in cardiovascular events or toxicity secondary to nicotine therapy. Two large studies of men with documented coronary artery disease with up to 10 weeks of nicotine therapy showed lower rates of cardiovascular endpoints and events in the nicotine-treated group<sup>73</sup>. A study of myocardial perfusion in men with coronary artery disease showed that cigarette smoking was associated with significantly greater myocardial perfusion deficits than nicotine therapy alone, suggesting that such a perfusion defect is due to factors from tobacco other than nicotine. In reviewing the available clinical trial literature and data reported to the FDA as of 1998, Rennard and colleagues concluded: "the available clinical trial and the clinical experience reported to date are consistent with the relative safety of transdermal nicotine in stable patients with cardiac disease."



**Figure 3.** Systolic blood pressure change from the MCI pilot trial.

**MCI Pilot Study<sup>47</sup>:** Data from our recently published MCI trial (conducted in non-smoking individuals) are presented in Figure 3. An examination of the change in systolic blood pressure revealed a significant reduction in systolic blood pressure compared to placebo treatment. By day 182, the placebo group showed an average increase of 9.6 mmHg in SBP compared to a reduction of 4 mmHg in the nicotine-treated group. There

was a small reduction in diastolic blood pressure by day 182 in the nicotine-treated group. An examination of the change in pulse showed no overall treatment effect ( $p = 0.51$ ).

**Cerebrovascular Safety:** Smoking is a preventable risk factor for ischemic stroke and some preclinical studies have suggested potential mechanisms by which smoking and/or nicotine might increase the risk of ischemic stroke<sup>75-77</sup>. However, a large meta-analysis of 35 smoking cessation trials did not find any increased incidence of stroke in nicotine replacement therapy users<sup>72</sup>.



**Conclusion regarding cardio- and cerebrovascular safety:** As the subjects to be enrolled in this study will be nonsmokers selected for the absence of significant cardiovascular, cerebrovascular disease, or diabetes, we believe that the cardiovascular and cerebrovascular risk profile of transdermal nicotine in such patients is excellent.

**Insulin Sensitivity:** There have been some epidemiologic studies suggesting a positive relationship between smoking and insulin resistance<sup>78</sup> although some studies are contradictory<sup>79</sup>. Some investigations have suggested that changes in insulin sensitivity may be restricted to smokers who are also diabetic<sup>80</sup>. One study that did examine long-term nicotine use without cigarette smoking showed that nicotine gum users had higher circulating leptin levels that were negatively correlated with the degree of insulin sensitivity<sup>81</sup>. However, the subjects were also recent ex-smokers, complicating interpretation of these results and acute administration of nicotine during the study did not change circulating leptin levels. Contradictory results were also seen in studies of smokeless tobacco use on cardiovascular risk factors and insulin levels with one study of heavy users finding impaired measures of glucose tolerance<sup>82</sup> while another study did not<sup>83</sup>. At this point, it is not conclusive that nicotine use alone in nonsmokers is associated with changes in insulin sensitivity.

**Fetal Development:** The FDA does not recommend the use of transdermal nicotine patches during pregnancy. At present the risks and effects of transdermal nicotine patches to a developing human fetus are not fully known. Therefore, if participants are of childbearing age we will strongly recommend the use of effective contraception during this study. Participants that are pre-menopausal and of childbearing age will be required to take a urine pregnancy test prior to randomization (Visit 2) and at each subsequent visit throughout the study (Visits 3, 4, 5, 6, 7). Participants that are post-menopausal will not be required to take a pregnancy test. If at any point the participant believes they may be pregnant, they will be advised to discontinue use of the study medication and inform the study coordinator immediately.

**Carcinogenesis:** Long-term epidemiologic studies of oral tobacco use suggest that the nitrosamine content of tobacco is critical to determining the cancer risk from non- smoke related tobacco use, rather than nicotine<sup>73</sup>. Whether nicotine can act as a permissive agent to encourage the development of cancer is unclear, but it does not seem to have any effect unless co-administered with tobacco<sup>73</sup>. Nicotine by itself does not appear to be carcinogenic<sup>84</sup>, and is therefore not expected to increase risk of breast, colon cancer, lymphoma, or ovarian cancer recurrence.

**Abuse Potential:** We believe that the probability that the subjects in this study might be prompted by their participation to begin to use nicotine containing products or tobacco is extremely low. There have been no cases reported in the medical literature of primary abuse by never smokers of nicotine replacement therapies. Furthermore, there are no cases reported of ex-smokers taking up nicotine replacement therapy and becoming addicted or dependent. Additional reasons for our belief that the risk of abuse of transdermal nicotine in this population include:

1. Nicotine replacement therapies have an extremely low abuse liability<sup>85</sup>; nicotine patches have some unpleasant side effects and therefore are unlikely to be reinforcing.

2. A study showed that experimental administration of tobacco did not induce ex-smokers to relapse into smoking<sup>86</sup>. In another study<sup>85</sup>, when non-smokers and ex-smokers were followed after participating in a study of nicotine gum administration, no subjects were found to be smoking or using other nicotine products three months following completion of the study.
3. An important characteristic of all drugs that produce dependency is the pharmacokinetic parameters associated with the route and form of administration<sup>87</sup>. With respect to nicotine, researchers of the NIDA Addiction Research Center<sup>88</sup>, as well as others in the field<sup>89-92</sup>, have reported that the slower absorption of nicotine offered by the transdermal patch relative to tobacco products substantially reduces the likelihood of nicotine dependence in users of the patch. This was supported by a study describing a double-blind placebo-controlled study investigating the therapeutic potential of the transdermal nicotine patch for patients suffering from ulcerative colitis<sup>73</sup>. Although all of the subjects were adults and many former tobacco users, despite 26 weeks of daily applications of 15 mg nicotine patches, no withdrawal symptoms were reported from these patients following discontinuation of the patch. In addition, a crossover trial evaluating the "liking" rating for the patch (22mg or 44 mg/24hr) in adults found no difference in scores between the active and placebo systems<sup>93</sup>.
4. We have administered intravenous and/or transdermal nicotine and structurally related nicotinic agonists over the past 17 years to several hundred non-smoking subjects including young and elderly normal volunteers, patients with Alzheimer's disease, and patients with Parkinson's disease. Perhaps most importantly, in our recently completed MCI trial<sup>47</sup>, no withdrawal symptoms were reported by subjects or informants nor were any subjects reported to be continuing to use nicotine after the study was completed. We have not had a single subject take up tobacco use as a consequence of study participation.

The safeguards that we have instituted that are described above taken in conjunction with data documenting that the administration of nicotine via non-tobacco routes is not associated with abuse liability, suggests that the incremental additional risk to subjects for tobacco use over and above their background use rate is likely to be very small.

**Minimization of risks associated with psychological and cognitive testing:** psychological and cognitive testing will take place over the period of 1 day for each study visit. Participants will be free to take as many breaks as needed to avoid exhaustion. The PI/study physician (Dr. Newhouse) will review the results of all behavioral tests and will handle any clinically significant results in a clinically appropriate manner.

**Minimization of risks associated with venipuncture to obtain DNA for genetic testing:** the risks of blood draw include pain from the needle, bruising or infection at the site of venipuncture, or fainting as a response to blood draw.



**Tolerability & Safety of Nicotine Treatment:** At each visit we will collect vital signs (blood pressure, pulse, respirations, etc) and weight. Tolerability and safety will be determined by counting specific adverse events, counting dropouts due to adverse events, and by determining how often there is a need to reduce the dose of nicotine as determined by the participant and the study physician. Adverse events will be recorded and categorized by body system, event type, attribution, frequency, severity, and course.

**Potential Problems/Alternative Approaches:** Medication intolerance may occur for some subjects. We have designed the medication titration schedules such that subjects who are intolerant of the full dose may still continue on the study at lower dose. Data analysis will consider dose as a covariate in the efficacy analysis and/or will be modified to utilize maximum tolerated dose as the independent variable.

**Risk/Benefit Ratio:** When the safety record outlined above is considered, the risks of participation in this study are low. The risks mainly consist of temporary side-effects from the nicotine and/or the transdermal patch that do not constitute a serious danger. Long-term cardiovascular, cerebrovascular, and neurological safety of transdermal nicotine appears to be very favorable. Subjects may benefit from cognitive improvement associated with persistent CRCI. The benefits to society of greater knowledge about the treatment of the cognitive changes associated with chemotherapy in breast cancer patients and their possible amelioration, considering the human and economic costs of this disorder, would appear significant. Overall the risk/benefit ratio appears to be in favor of conducting this study.

## **VII. Adverse Event Reporting**

Adverse events associated with the study are communicated to the Principal Investigator on a weekly basis, as they occur. Weekly review occurs of all participants involved in the study for any evidence of adverse events or difficulties with study medication or procedures.

The Vanderbilt University Institutional Review Board adverse event reporting system will be used. These reports will be forwarded to the office of the IRB within 5 days of the. This will be the responsibility of the Principal Investigator. The IRB will make a determination as to whether additional reporting requirements are indicated.

All adverse event reports will be reviewed on their presentation for severity and frequency and examined within the overall context of protocol specific adverse events. Reviews of protocol specific adverse events will be performed no less than annually.

## **VIII. Study Withdrawal/Discontinuation**

All participants will be free to withdraw from the study at any point without repercussions. Participation in this study will not change current cancer care.

## IX. Statistical Considerations

**Sample Size Justification:** We used average pre-chemotherapy and post-chemotherapy FACT-Cog scores (provided by Dr. Lynne Wagner) to estimate an expected effect size (Pre-chemotherapy mean= 64.57, SD=12.16; Post-chemotherapy mean= 58.51, SD=14.55; Effect size  $d=0.44$  or  $f=0.23$ ). Based on the data provided, we would need 32 participants to see an effect size of  $f=0.23$ . Based on previous nicotine treatment studies conducted by the lab we anticipate a dropout rate of 10-20%<sup>47</sup>; therefore we will target recruitment at 40 participants.

**Statistical Analysis Plan:** All outcome variables of interests are shown in Table

6. For Specific Aim 1, mixed-models repeated measures ANOVA will be used to assess the interaction of treatment group (nicotine, placebo) with PCI FACT-Cog score over time (Visit 2, Visit 3, and Visit 4). In addition, unpaired t-tests will be used to conduct a pre-treatment/baseline (Visit 2) and post-treatment (Visit 4) comparison, as well as a loss of effect comparison for the FACT-Cog PCI component. We hypothesize that nicotine treatment will improve FACT-Cog scores in breast cancer, colon cancer, lymphoma, or ovarian cancer patients with persistent CRCI over 6 weeks of treatment compared to placebo.

For Specific Aim 2, mixed-models repeated measures ANOVA will be used to assess the interaction of treatment group (nicotine, placebo) with CPT reaction time standard error divided by interstimulus interval (a measure of variability of reaction time) over time (Visit 2, Visit 3, and Visit 4). In addition, unpaired t-tests will be used to conduct a pre-treatment/baseline (Visit 2) and post-treatment (Visit 4) comparison, as well as a loss of effect comparison for the CPT reaction time standard error divided by interstimulus interval. We hypothesize that nicotine treatment will improve performance (reduce reaction time variability) the CPT in breast cancer, colon cancer, lymphoma, or ovarian cancer patients with persistent CRCI over 6 weeks of treatment compared to the placebo group. Differences for rates of adverse events or other safety abnormalities between groups will be assessed using chi-square analysis.

## X. Privacy/confidentiality Issues

All departments and laboratories involved in this study will follow procedures to ensure that no reasonable chance of the participant's data can be linked to her/his identity. Confidentiality will be sincerely attempted, but cannot be guaranteed. All research data will be kept confidential and will be identified by ID number rather than name. Only research personnel will have access to participants' files. Data will not be released to any source without written

Table 6. Primary and Secondary Outcome Variables

Measure	Task/Test	Outcome Variable
Primary	FACT-Cog	PCI Component Score (Increase in score = improvement)
	CPT	Reaction time Standard Error/Interstimulus Interval
Secondary	CRT	Reaction Time (ms) (Lower score = better performance)
	CFF	Correct Detections (Higher score = better performance)
	Buschke SRT	8 Trial Total Recall, Immediate/Delayed Recall (Higher score = better performance)
	Detection Task	Speed of Performance (ms) (Lower score = better performance)
	Identification Task	Speed of Performance (ms) (Lower score = better performance)
	One Back Task	Accuracy of Performance (Higher score = better performance)
	Two Back Task	Accuracy of Performance (Higher score = better performance)
	Groton Maze Learning Test	Total # of Errors (Lower score = better performance)
	Set-Shifting Task	Total # of Errors (Lower score = better performance)

consent from the participant or the participant's caregivers. Participants and their caregivers will be informed that they may withdraw from the study at any time without negative consequences.

**Cognitive and Psychological Test Data:** Electronic databases containing identifiable participant information will be password protected. Written information containing participant identifiers (informed consent, lab results, participant payment, etc.) will be stored in locked file cabinets in offices within the Center for Cognitive Medicine separate from other data. Only the PI and authorized key study personnel will have access to this information. Participants will be assigned an alphanumeric code that will be used to label all research data. Information will not be entered directly into a participant's medical record or shared with their insurance company.

After the study ends, the PI will continue to maintain (for future analysis, quality control checks, etc.) the original forms and questionnaires in locked file cabinets, and the DNA samples will continue to be stored in the Vanderbilt University DNA Resources Core.

**Genetic Research and Storage of Genetic Material:** The de-linking of the sample from the participant occurs at the time the blood is sent to the Vanderbilt University DNA Resources Core. Samples are labeled with barcodes, which are linked to the participant's ID number, not name, in the Core's Oracle database. Bar code labels affixed to each sample vial will contain the following information: sample ID# (to preserve confidentiality), date of collection and processing, total initial volume collected, volume, aliquot number, freezer, shelf, rack, box, location in the box. A bar code label will be used on the sample tracking form. Vanderbilt University DNA Resources Core will not have information regarding the participant's name and thus will be unable to link the DNA analysis results to the person.

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